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TI Histamine receptors
AU Watanabe, Takehiko; Yanai, Kazuhiko; Fukui, Hiroyuki
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TI Histamine H1 receptor-mediated inhibition of potassium-evoked release of 5-hydroxytryptamine from mouse forebrains.
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TI IMPROGAN, A HISTAMINE DERIVATIVE, INDUCES ANTINOCICEPTION IN HISTAMINE
RECEPTOR - DEFICIENT MUTANT MICE.
AU Hough, L. B. (1); Nalwalk, J. W. (1); Mobarakeh, J. I.; Yanai, K.; Stadel,
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 156.15. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002 Society for Neuroscience.
DT Conference

TI Activation of spinal histamine H3 receptors inhibits mechanical nociception
AU Cannon, Keri E.; Nalwalk, Julia W.; Stadel, Rebecca; Ge, P.; Lawson, D.;
SO European Journal of Pharmacology (2003), 470(3), 139-147

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Histamine H1 receptor-mediated inhibition of potassium-evoked release of 5-hydroxytryptamine from mouse forebrains

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Abstract

The release of endogenous serotonin and dopamine from slices of mouse forebrains induced by high extracellular K^+ was examined in histamine H1 receptor knockout mice. The release of 5-hydroxytryptamine (5-HT) evoked by 30 mM K^+ significantly decreased in the presence of 10–50 μM histamine in wild-type mice, but was not inhibited in the mutant mice. Histamine H1 receptor-mediated inhibition of serotonin release in wild-type mice was also observed in the presence of thioperamide, an H3 antagonist. From these data, we postulate that endogenous histamine indirectly inhibits the release of 5-HT through H1 receptors in addition to H3 receptors. The treatment of 2 μM tetrodotoxin could partly abolish the effects of histamine on K^+-evoked 5-HT release. Bicuculline, a $GABA_A$ antagonist, could reverse the histamine-induced inhibition of 5-HT release in wild-type mice, suggesting that H1 receptors facilitate the release of GABA, which in turn inhibits 5-HT release through $GABA_A$ receptors. The difference in the effects of *d*- and *l*-chlorpheniramine on K^+-evoked 5-HT release in wild-type mice further supports the evidence of the function of H1 receptor modulating 5-HT release.

Keywords: Histamine; Histamine H1 receptor; 5-Hydroxytryptamine release; Anxiety; Brain slice; Antidepressants; Chlorpheniramine

1. Introduction

Since histaminergic neurons were demonstrated in the brain [24,34], their functions have been investigated extensively in animals [10,11,16,26,28,33]. Brain histamine is thought to affect arousal, the wake-sleep cycle, appetite control, seizures, learning and memory, aggressive behavior, and emotion. These data were mainly obtained from rodents through classical pharmacological experiments using enzyme inhibitors and histamine receptor antagonists and agonists [22,35]. With gene targeting, one can practically knock out a gene in vivo and create a mutant organism that completely lacks the gene product [8,17]. We generated mutant mice lacking histamine H1 receptors by using gene targeting [13]. No specific binding of [^{3}H]pyrilamine was seen in the brains of homozygous mutant mice. In previous studies, mutant mice showed several behavioral changes when compared to wild-type mice [38,39]. We have also observed that the turnover rate of 5-hydroxytryptamine (5-HT), defined by the ratio of 5-hydroxyindoleacetic acid (5-HIAA)/5-HT, increased significantly in the H1 receptor null mice.

It is well known that some antidepressants are very potent competitive histamine H1 antagonists [26]. For example, doxepin, the most potent of this class, is about 60 times more potent than the classical antihistamine, diphehydramine, in radioligand binding studies. The antidepressant effects are thought to be attributable to the blockade of monoamine transporters. The blocking of H1 receptors is likely to merely cause side effects such as sedation, drowsiness and appetite

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increase. However, a possible contributory role of histamine neurons to stress, aggressive behavior and depression has been suggested from animal experiments. Some H1 antagonists are known to reduce the duration of immobility in the forced swimming test [19]. H1 receptor knockout mice showed less aggressiveness when compared to wild-type mice. It is still not conclusive whether the H1 antagonism by antidepressants is partly attributed to their antidepressant actions.

The discovery of histamine H3 receptors has uncovered a role for histamine in the regulation of histamine synthesis and its presynaptic release as well as the release of serotonin, norepinephrine and acetylcholine [1,5,29,30]. In all cases, the effects of histamine on the release were inhibitory and several histamine receptor antagonists were used to demonstrate the function of H3 receptors in previous reports [31]. Although drugs primarily interact with specific target molecules, they also have other actions. The data obtained by pharmacological experiments should be re-evaluated from the point of view of specificity [36].

In the present study, brain slices of the mutant and wild-type mice were superfused with a Ringer bicarbonate solution, and the endogenous release of dopamine and 5-HT was measured. The purpose of this study is to reveal whether the activation of H1 receptors is participating in the regulation of the release of dopamine and 5-HT in the mouse brain.

2. Materials and methods

2.1. Animals

Male mutant mice (−/−) and wild-type mice (+/+) weighing 30–35 g were used. All experiments were performed on animals between the ages of 2–5 months. These mice were bred in our laboratory. Approximately 10 mice were housed as a group in one cage. They were housed at a constant temperature (22 ± 3°C) with a constant relative humidity (55 ± 10%) on an automatically controlled light cycle (light on, 6:00–18:00) and had free access to food and water. Their brains were removed, and the binding of [^{3}H]pyrilamine was measured to verify whether the H1 receptor subtype was absent in the mutant mice. Several mice were selected and analyzed by PCR of genomic DNA from tail biopsies for the presence of the H1 receptor mutant allele.

2.2. PCR

Mice were selected and analyzed by PCR of genomic DNA from tail biopsies with slight modifications of the previous method [13]. The mutant allele was detected using 5′-TGAAGTATCTGGCTCTGAGTGG-3′ (5′-primer, 5′-upstream of H1 receptor gene) and 5′-TCTATCGCCTTCTTGACGAG-3′ (3′-primer complementary to a neo^r gene sequence) with the following PCR conditions: 35 cycles of 1 min at 95°C, 1 min at 60°C, 2 min at 72°C (PCR band; ≈0.98 kbp). The wild-type allele was also detected using 5′-TGAAGTATCTGGCTCTGAGTGG-3′ (5′-primer as the same as mutant allele) and 5′-CCATCGATGGCTCCCTCCCTGGGAG-3′ (3′-primer complementary to H_1-receptor gene) (H_1-receptor PCR band; 1.2 kbp) [12].

2.3. [^{3}H]Pyrilamine binding to tissues

The cerebellum was dissected from mutant and wild-type mice. Tissues were homogenized in a Polytron (setting 5, 20 s) in ≈20 volumes of ice-cold Na^+/K^+ phosphate buffer (50 mM, pH 7.5), and the homogenate was centrifuged twice at 50 000*g* for 20 min. The final pellet was resuspended in 40 volumes of the ice-cold buffer. Incubation with [^{3}H]pyrilamine (Amersham, England) was carried out at 25°C for 30 min, and the reaction was terminated by addition of 5 ml of buffer and rapid filtration on a glass fiber filter (GF/B). Specific binding was defined as the radioactivity bound after subtraction of nonspecific binding, determined in the presence of 2 μM triprolidine [4,40]. The amounts of H1-receptor binding in the mutant (−/−) and wild-type (+/+) mice were 5.5 ± 4.6 and 247.9 ± 66.3 fmol/mgprotein/nM, respectively.

2.4. Measurements of endogenous dopamine and 5-hydroxytryptamine release from brain slices

Forebrain slices (450 μm thickness) including cerebral cortex, amygdala, hippocampus, thalamus and hypothalamus were obtained using a McIlwain tissue chopper and the brain slices of mutant and wild-type mice were incubated for 5 min at 4°C with a physiological salt solution. After washing with a physiological solution, the tissue samples were transferred with the aid of a Gilson pipette to a superfusing chamber (0.5 ml capacity). Then tissues were superfused with the physiological salt solution (K^+ = 2.2 mM, 37°C) at a rate of 80 μl/min (peristaltic pump, Ismatec MV-MS/CA). The physiological salt solution was composed as follows (mmol/l): NaCl 120, KCl 1, $MgSO_4$ 1.2, $NaHCO_3$ 27.5, D-glucose 10, $CaCl_2$ 1.5, KH_2PO_4 1.2; it was gassed with O_2/CO_2 (95/5, v/v).

The slices were first perfused with the salt solution (K^+ = 2.2 mM) for 60 min and then superfused for 30 min with a solution containing 31.2 mM K^+ (composition in mM: NaCl 91, KCl 30, $MgSO_4$ 1.2, $NaHCO_3$ 27.5, D-glucose 10, $CaCl_2$ 1.5, KH_2PO_4 1.2). After a 45-min re-perfusion of the physiological salt solution (2.2 mM K^+), the brain slices were again stimulated for

30 min with a solution containing 31.2 mM K^+. Then, it was again superfused with the physiological salt solution for 60 min. Unless indicated otherwise, the drugs were added at 22.5 min before the second stimulation (S2) and were present until the end of each experiment. The samples of perfusate were collected with a fraction collector at 5-min intervals and monoamines and their metabolites in the perfusate were measured using an HPLC system. The first and second K^+-evoked releases were denoted as S1 and S2, respectively.

Monoamines and their metabolites were separated using an HPLC system at 30°C on a reverse-phase analytical column (ODS-80^{TS}, 4.6 mm ID × 15 cm), and detected by an electrochemical detector (Model ECD-100, Eikom Co., Kyoto, Japan) [38]. The column was eluted with a 0.1 M sodium acetate citric acid buffer (pH 3.5) containing 15% methanol, 200 mg/l sodium *l*-octanesulfonate, and 5 mg/l Na_2-EDTA. The following monoamines and their metabolites were measured: dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, 5-HT (serotonin), and 5-HIAA.

2.5. Analysis of data

All chromatographic data of HPLC were stored in an Apple Macintosh computer with a PowerChrom system (ADInstruments). For each experiment, the peaks of dopamine and 5-HT in 45 samples were analyzed with an Apple Macintosh computer. The concentration of dopamine and 5-HT in 45 samples of the perfusate was plotted as the function of time at the onset of the respective collection period. In order to quantify drug-induced effects on the neurotransmitter release, the ratio of the efflux in the collection periods from the first and second K^+-stimulation was determined in each experiment. The K^+-evoked release was calculated by subtraction of basal release from the total amount of efflux during stimulation and the subsequent 20 min. Basal release from brain slices was expected to decline exponentially. The basal amounts of the release during stimulation were estimated from the basal release for 5–25 min before the first stimulation, for 5–25 min before S2, and for 25–60 min after S2. The ratio of the efflux evoked by S2 and by S1 (S2/S1) was calculated to quantify drug-induced effects on the K^+-evoked release. The difference in the ratio of S2/S1 was analyzed by ANOVA followed by Dunnett's multiple comparison test, non-parametric Wilcoxon *t*-test, or Kruskal–Wallis test.

2.6. Chemicals

The following drugs were used: histamine (Sigma, St. Louis, MO), *d*-chlorpheniramine (Sigma), *l*-chlorpheniramine (a kind gift from Essex Japan Pharmaceutical Co. Ltd.), thioperamide (RBI, Natick, MA), tetrodotoxin (TTX) (Wako Chemical, Tokyo, Japan), famotodine (Sigma), bicuculline methiodide (RBI).

3. Results

3.1. The measurement of endogenous dopamine and 5-HT release from the slices of the mutant and wild-type mice forebrains

As observed in other experiments of superfusion, there was a large initial efflux of endogenous dopamine and 5-HT during the first 30 min [7,29]. A stable basal release was reached ≈ 30 min after the initiation of the experiments. As shown in Fig. 1, the K^+-evoked release of 5-HT from the slices of the mutant and wild-type mouse forebrains was plotted from 30 to 230 min. Potassium-evoked stimulation for 30 min produced a rapid increase in endogenous 5-HT release and DA release. The increase observed for about 60 min with our apparatus was probably due to the dispersion of flow (Fig. 1). For the 5-HT release, the ratios of S2/S1 in the wild-type and mutant mice were 40.1% ± 14.4% and 35.1% ± 10.3%, respectively. For DA release, the ratios of S2/S1 in the wild-type and mutant mice were 37.0% ± 10.7% and 28.7% ± 5.4%, respectively. The difference between the wild-type and mutant mice was not statistically significant (ANOVA followed by Dunnett's multiple comparison test).

3.2. The effects of histamine on the endogenous dopamine and 5-HT release from the slices of mutant and wild-type mouse forebrains

Since we could not observe any significant difference in the release of dopamine and 5-HT between the

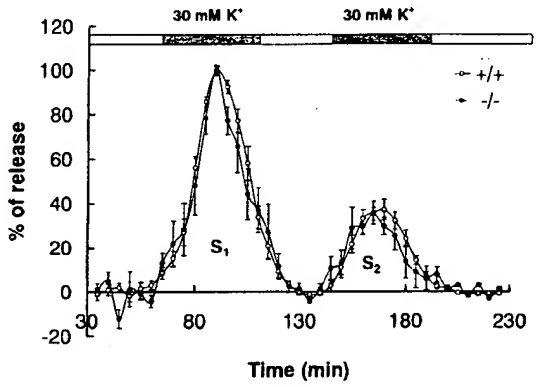

Fig. 1. Potassium-evoked 5-HT release from brain slices of the wild-type (○) and mutant mice (●) in the absence of histamine. The efflux of 5-HT from brain slices at every 5 min was plotted as the percentage of maximum release of S1. The data are expressed as the mean ± SEM from 6 wild-type and 6 mutant mice. Note that there is no significant difference in the K^+-evoked release of 5-HT between the wild-type and mutant mice.

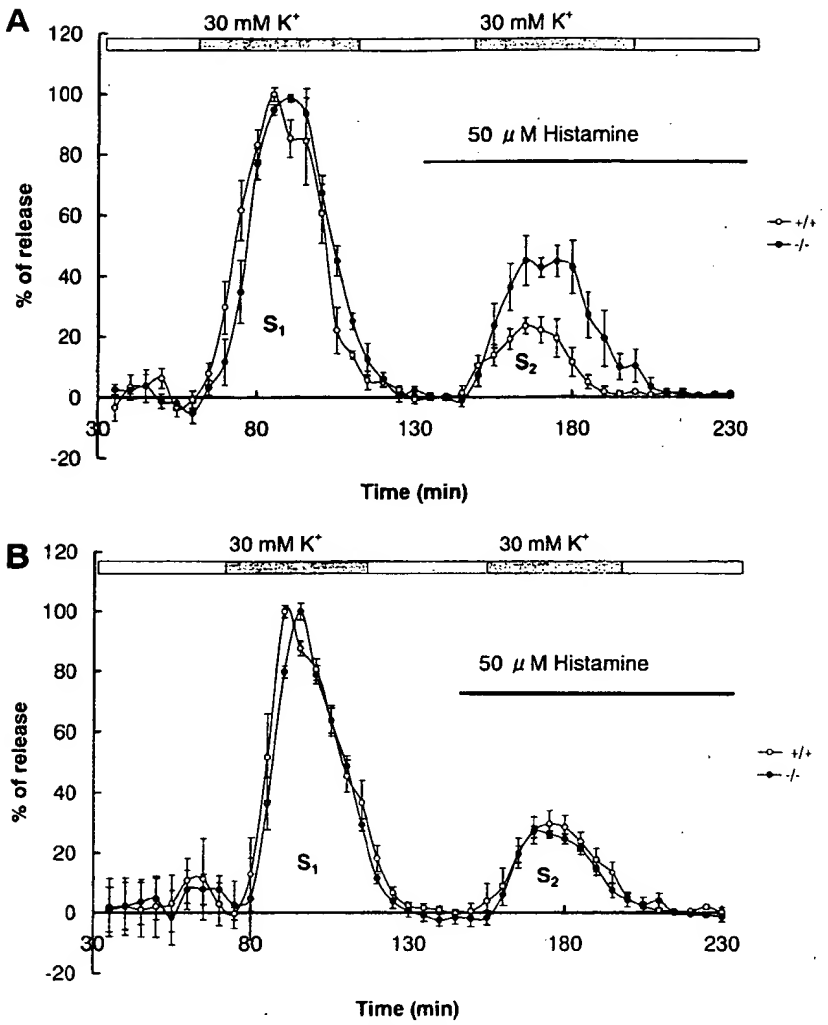

Fig. 2. The effects of 50 μM histamine on the 5-HT (A) and dopamine (B) release from the brain slices of the wild-type (○) and mutant mice (●). The data are expressed as the mean ± SEM from 6 wild-type and 6 mutant mice. Note that significant decrease in the K^+-evoked release of 5-HT was observed between the wild-type and mutant mice after treatment of 50 μM histamine.

wild-type and mutant mice, the effects of histamine on the release of 5-HT and DA were examined in the brain slices of the two groups. In the presence of 50 μM histamine, 30 mM K^+-evoked release of 5-HT decreased significantly in wild-type mice, while the treatment of histamine did not affect the 5-HT release in the mutant mice (Fig. 2(A)). The effects of the histamine treatment on 5-HT release were dose-dependent, and the treatment of over 10 μM histamine could significantly decrease the 5-HT release (Fig. 3). On the contrary, the K^+-evoked release of dopamine in the two groups was not significantly affected by the treatment of histamine (Fig. 2(B)). These data suggested that the K^+-evoked release of 5-HT might be decreased by the activation of H1 receptors.

3.3. The effects of thioperamide on the endogenous 5-HT release from the slices of the mutant and wild-type mouse forebrains

It is well known that the activation of histamine H3 receptors at the presynaptic sites of 5-HT neurons decreases the 5-HT release [29]. In order to distinguish the effects of the H1 receptors from those of H3 receptors, the effects of thioperamide (an H3 antagonist) on the K^+-evoked 5-HT release were examined in wild-type mice. The treatment of thioperamide slightly increased the K^+-evoked 5-HT release at a range of 0.2–2 μM, but the effects were not statistically significant (data not shown, Dunnett's multiple comparison test). In the presence of 2 μM thioperamide, the ratio of

S2/S1 for 5-HT release in wild-type mice was 58.1% ± 9.2% ($n = 5$), and the ratio decreased to 41.9% ± 11.4% by the addition of 50 μM histamine ($n = 6$). The histamine-induced decrease of 5-HT release was statistically significant (non-parametric Wilcoxon t-test, Kruskal–Wallis test). The treatment of histamine could decrease the K^+-evoked 5-HT release even in the presence of the H3 antagonist, indicating that H1 receptor-mediated inhibition of 5-HT release was also working in the brain in addition to the H3 receptor-mediated inhibition.

3.4. The effects of tetrodotoxin and bicuculline on the endogenous 5-HT release from the slices of wild-type mice forebrains

The effects of TTX and bicuculline on the 5-HT release from the brain slices of wild-type mice were examined to characterize the histamine-induced inhibition of 5-HT release. The treatment of TTX increased the ratio of S2/S1 ratios dose-dependently (at a range of 0.2–5 μM). After treatment of 2 μM TTX, the ratios of S2/S1 in the absence and presence of 50 μM histamine were 45.9% ± 8.0% ($n = 5$) and 37.6% ± 17.6% ($n = 5$), respectively. In the presence of 2 μM TTX, the endogenous release of 5-HT was expected to decreased by the treatment of 50 μM histamine, but the decrease was too small to be statistically significant.

The treatment of bicuculline, a $GABA_A$ antagonist, similarly potentiated the 5-HT release from brain slices of wild-type mice at doses of 2 and 10 μM. After treatment of 2 μM bicuculline, the ratios of S2/S1 in the absence and presence of 50 μM histamine were 56.6% ± 12.1% ($n = 5$) and 57.3% ± 7.3% ($n = 5$), respectively. In the presence of 2 μM bicuculline, the treatment of 50 μM histamine had no effect on the 5-HT release from the brain slices of wild-type mice. These data suggest that the H1-receptor-mediated regulation of 5-HT release is sensitive to the treatment of bicuculline.

3.5. The effects of histamine H1 and H2 antagonists on the endogenous 5-HT release from the slices of wild-type mice forebrains

To confirm the H1 receptor-mediated inhibition of 5-HT release, the effects of d-chlorpheniramine, l-chlorpheniramine and famotidine on the 5-HT release were examined in wild-type mice brains. Stereoselectivity of the binding has been shown previously by inhibition of [^{3}H]pyrilamine binding in vitro and in vivo in guinea pig brain, the d-isomer being about 100 times more potent than the l-isomer [4,40]. As shown in Fig. 4, the treatment of d-chlorpheniramine was able to enhance the K^+-evoked release of 5-HT from brain slices dose-dependently. On the contrary, l-chlorpheniramine, a less active isomer of the H1 antagonist, did not increase the 5-HT release at concentrations of 0.2–20 μM. The treatment of 200 μM l-chlorpheniramine enhanced the K^+-evoked 5-HT release significantly. The ratios of S2/S1 in the absence and presence of 20 μM famotodine were 42.2% ± 15.4% ($n = 12$) and 45.1% ± 14.5% ($n = 3$), respectively. In the presence of 20 μM famotidine, the treatment of 50 μM histamine did not affect the 5-HT release from the brain slices of wild-type mice.

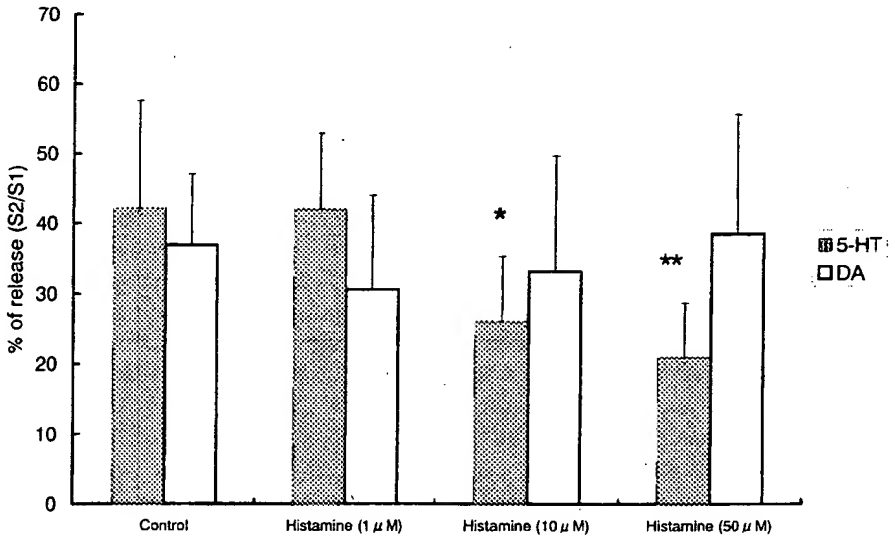

Fig. 3. Dose-dependent effects of histamine on the K^+-evoked release of 5-HT (hatched column) and dopamine (open column) in the wild-type mice. The release of dopamine was not affected by the treatment of histamine. The % release (S2/S1 ratio) is expressed as the mean ± S.D. of the percent ratio of S2/S1 from 6 to 12 determinations. (*) $P < 0.05$, (**) $P < 0.01$, statistical significance of difference between the control and histamine treatment by ANOVA followed by Dunnett's multiple comparison test.

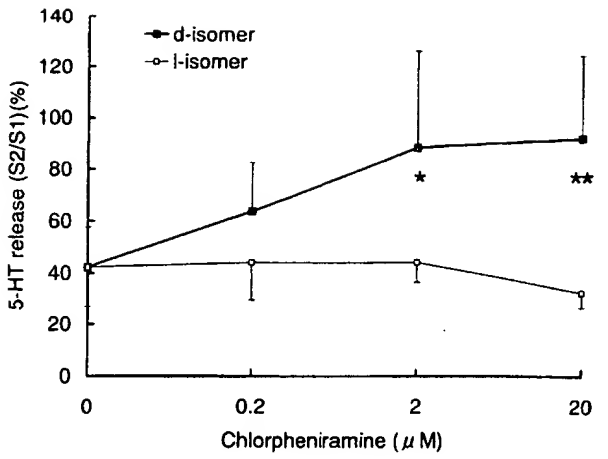

Fig. 4. The effects of *d*-chlorpheniramine (■) and *l*-chlorpheniramine (□) on the K^+-evoked 5-HT release in the wild-type mice. Note that the treatment of *d*-chlorpheniramine dose-dependently increased the K^+-evoked 5-HT release in the wild-type mice. The % release (S2/S1 ratio) is expressed as the mean ± S.D. of the percent ratio of S2/S1 from 4 to 12 determinations. (*) $P < 0.05$, (**) $P < 0.01$, statistical significance of difference between the *d*- and *l*-chlorpheniramine treatment by ANOVA followed by Dunnett's multiple comparison test.

4. Discussion

We have attempted to reveal the functional role of the histamine H1 receptor-mediated neurotransmission using a new technology of gene targeting. We examined the behavior of homozygous mutant mice using several tasks [13,38,39]. The mutant mice showed impaired locomotor activity and reduced exploratory behavior when placed in a new environment. They were significantly less aggressive than the wild-type mice in a resident-intruder aggression test. The data obtained by this study of the knockout mice are similar to those obtained by classical pharmacological tools. These results confirm that histamine modulates various neurophysiological functions, such as locomotor activity, emotion, memory and learning, nociception and aggressive behavior, through the activation of the H_1 receptor. In accordance with behavioral abnormalities observed in mutant mice, the turnover rate of 5-HT, defined by the ratio of 5-HIAA/5-HT, significantly increased among the mutant mice [38].

In order to reveal the mechanism of controlling the release of 5-HT through H1 receptors, possible modulatory effects of histamine on potassium-evoked monoamine release from slices of mutant and wild-type mice were investigated in this report. Although the dopamine release did not change, 10–50 μM histamine significantly inhibited the release of 5-HT from brain slices of the wild-type mice. On the other hand, the release of 5-HT was not affected by treatment with 50 μM histamine in the H_1-receptor null mice. The results provide the first striking evidence that histamine can inhibit the release of 5-HT through H_1 receptors in addition to the H3 receptor-mediated inhibition. These data further suggest that 5-HT release in mutant mice is augmented because of the lack of H1-receptor-mediated inhibition of 5-HT release.

When TTX was treated with brain slices, the histamine-evoked inhibition of 5-HT release from brain slices of wild-type mice was partly abolished. TTX blocks voltage-dependent sodium channels in neuronal tissues. Exocytotic neurotransmitter release produced by nerve stimulation and nerve action potentials was diminished by the administration of TTX. Thus, these data suggest that major parts of the histamine-induced inhibition of 5-HT release act indirectly on the serotonergic neurons. Hence, the inhibition is likely to be indirect, probably mediated by other transmitters which, in turn, inhibits 5-HT release. In this study, bicuculline, a $GABA_A$ receptor antagonist, was used to examine the possible involvement of GABAergic neurotransmission in histamine-induced inhibition of 5-HT release. Bicuculline completely reversed the inhibition of 5-HT release induced by histamine. These findings suggest that H1 receptors, located postsynaptically on intrinsic perikarya or presynaptically on varicosities, facilitate the GABA release, which, in turn, inhibits 5-HT release. The same mechanism for H3 receptors modulating the release of ACh has been proposed [9]. It is well known that both histamine H1 receptors and serotonergic innervations are rich in the cortex and amygdala. Their postulated interactions through GABAergic interneurons or ending could mostly occur in the regions of cortex and amygdala included in the brain slices.

Histamine H1 receptors are also present on glial cells besides being located on neurons [16,23,32,37]. Several cell lines derived from glial cells express H1 receptors whose binding properties are quite similar to those present in the mammalian brain. It has been recently reported that glial cells are involved not only in terminating the action of inhibitory and excitatory amino acids by taking up and metabolizing, but are also active in synaptic transmission by releasing neuroactive substances [32]. In line with the active function of glial cells, histamine stimulates GABA release through H1 receptors located on glial cells by increasing intracellular Ca^{2+} mobilization. The mechanism of GABA release in glial cells is thought to be related to change in transmembranal Na^+ gradients and reversal of GABA carrier transport due to stimulation of the plasma membrane Na^+/Ca^{2+} exchange. The mechanism for histamine-induced inhibition of 5-HT release is likely to be related to an active role for glia modulating the GABA release (Fig. 5).

Diphenhydramine and hydroxyzine, the first-generation antihistamines, are occasionally used as anxiolytics. In our previous report, the light/dark distribution and the elevated plus-maze test were used to investigate whether the H1 receptors were involved in anxiety. We could not observe any difference in the light/dark exploration between the H1 receptor knockout mice and the wild-type mice. The elevated plus-maze test is based

on the apparent natural aversion of rodents to open and high spaces, and is employed for measurement of anxiety by many research laboratories [6,14,18]. In this test, the mutant mice showed the prolonged transfer latency, indicating that the mutant mice were less fearful than the wild-type mice. These data suggested that histamine might be acting through H1 receptors as a facilitatory neurotransmitter in the control of anxiety. In accordance with this, Frisch et al. recently reported that bilateral lesions of the tuberomammillary E2-subregion could induce anxiolytic-like effects in the rats, as indicated by increased and decreased sojourn times on the open and enclosed arms of the elevated plus-maze, respectively [6].

Various H1 antagonists are known to suppress isolation-induced fighting in mice or muricide activity in rats [2,20,21], although there are several conflicting views on the role of histamine H1 receptors in control of aggressive behavior [25]. When the H1KO and the wild-type mice were housed as a group, the mice of one group are not more aggressive than those of the other. However, after several months of isolation and in the presence of an intruder, the mutant mice were significantly less aggressive than the wild-type mice. The results of the aggression test are consistent with the notion that H1 receptor-mediated neurotransmission may be related to aggressive behavior. We also observed that the turnover rate of 5-HT, defined by the ratio of 5-HIAA/5-HT, was significantly increased in the H1 receptor-deficient mice. Several studies have revealed an association between aggressive behavior and a reduction in the activity of the serotonergic system. In rodents and primates, aggressiveness is increased after inhibition of serotonin synthesis, destruction of serotonergic neurons, or the disruption of 5-HT1B receptor gene [3,27]. The serotonergic neurotransmission in the H1 receptor null mice might be augmented in accordance with the serotonergic mechanism of aggressive behavior.

The 5-HT release from the brain slices of the wild-type and mutant mice was compared in order to clarify whether the H1 antagonism is partly attributed to their antidepressant actions. Brain slices were superfused with Ringer bicarbonate solution, and the K^+-evoked release of 5-HT was measured. The release of 5-HT evoked by 30 mM K^+ was significantly decreased in the presence of 10–50 μM histamine in the wild-type mice, while that was not inhibited in the mutant mice. H1 receptor-mediated inhibition of serotonin release in the wild-type mice was also observed in the presence of an H3 anatgonist. From these data, we postulated that endogenous histamine physiologically inhibits the release of 5-HT through H1 receptors. From our studies, it was suggested that the blockade of H1 receptors could augument the release of 5-HT. The results provide the first neurochemical evidence regarding antidepressant effects of H1 receptor blockade, although there is a conflicting view on the role of H1 receptor in depression [15]. The difference is probably due to that of the acute and chronic effects.

Acknowledgements

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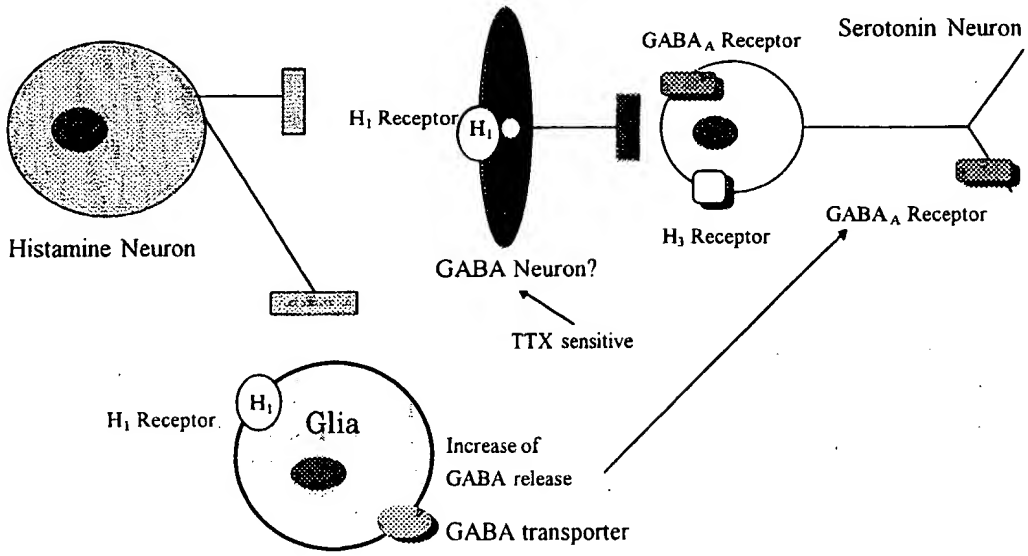

Fig. 5. A schematic representation of possible mechanisms for histamine H1 receptor-mediated inhibition of 5-HT release.

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